REMARKS

Claims 1-7, 9-12, 25-28 and 48-54 are pending in the subject application. Applicants note that the Examiner has withdrawn claims 11-12 from further consideration. Applicants have hereinabove amended claims 1, 11 and 25. Support for the amendments to these claims may be found, inter alia, in the specification as follows: Claim 1: page 11, lines 1 - 2 and page 24, lines 24-26; Claim 25: in claims 13 and 15 as filed and at page 7, line 21. The changes to claim 11 merely eliminate any multiple dependency. Applicants maintain that these amendments raise no issue of new matter, and respectfully request entry of this Amendment. Upon entry of this Amendment, claims 1-7, 9-12, 25-28 and 48-54, as amended, will be pending and under examination.

In view of the amendments and arguments set forth below, applicants maintain that the Examiner's objections and rejections have been overcome and respectfully request that the Examiner reconsider and withdraw same.

1. Specification, 35 USC §101 ; 35 USC §112 :

We note the Examiner has withdrawn the rejections previously made under 35 USC §101 and 35 USC §112.

2. Claim Objection under 37 CFR 1.75 (c) :

The Examiner has objected that claims 11 and 12 are improper because they depend from a multiple dependent claim. In response, applicants note that as amended hereinabove, the dependency of claim 11 has been amended and now depends only from claim 9. This objection is therefore

now moot. Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of objection and examine claims 11-12.

3. Claim Rejection under 35 USC §112 :

The Examiner has rejected Claims 25 to 28 and 48 because they depend on cancelled claims. In response, applicants note that as amended hereinabove, claim 25 has been amended to recite the process steps previously recited in method claims 13 and 15. This rejection is therefore now moot. Accordingly, applicants respectfully request that the Examiner reconsider and withdraw this ground of rejection.

4. Claim Rejections 35 USC §102

In response to the Examiner's objections under 35 USC §102, Applicant provides the following comments :

a)WO 00/53795 (*Katz et al*)

The Examiner considers that the disclosure of *Katz et al* (WO 00/53795) anticipates claims 1 to 3, 49, 50, 53 and 54, and claims 4 to 7, 9 to 12, 48, 51 and 52. The Examiner states that Applicant's arguments pointing out that the cells disclosed in "Katz II" are clearly different from those presently claimed, are not persuasive because the cells in "Katz II" are different from those disclosed in *Katz et al* (WO 00/53795). Specifically the cells disclosed in *Katz et al* (WO 00/53795) have telomerase activity. The Examiner agrees that *Katz et al* (WO 00/53795) does not disclose that the telomerase activity is at least 20% of HEK293T cells, but considers that unless demonstrated otherwise, the cells in *Katz et al* (WO 00/53795) are presumed to have

this activity for reasons of inherency.

Applicant submits that the telomerase activity reported in *Katz et al* (WO 00/53795) is NOT at least 20% of HEK293T cells, and further is not maintained throughout at least 130 population doublings

Katz et al (WO 00/53795) provides no information concerning the level of the telomerase activity or whether it is maintained through successive cell passages. It is merely stated that the TRAP assay kit was used and that telomerase activity was observed in the adipose-derived stem cells and in the positive controls.

Importantly, the US application from which *Katz et al* (WO 00/53795) claims priority (US 60/162,462 ; copy enclosed as EXHIBIT B) provides more detail with regard to the telomerase activity, particularly at pages 35 and 40 of the priority application.

First it is explicitly stated in the Katz priority application (US 60/162,462) that telomerase activity is measured in a heterogeneous, primary population of cells (page 40). There is no disclosure of telomerase activity after **130 population doublings** in **an isolated** multipotent cell as required by the claim.

Second, the Katz priority application (US 60/162,462) states that the telomerase activity in the cell population was "***qualitatively equivalent to a known positive keratinocyte cell line (NHOK) and bone marrow-derived mesenchymal stem cells***" (US 60/162,462, page 35, final paragraph).

The Katz priority application (US 60/162,462) thus discloses that the telomerase activity of the adipose-derived cells was qualitatively equivalent to two types of cells, namely :

- ***A telomerase-positive keratinocyte cell line (NHOK) and***
- ***bone marrow-derived mesenchymal stem cells***

It will be demonstrated below that neither of these cell types has the telomerase activity exhibited by the presently claimed cells, and that consequently, the cells disclosed in *Katz et al* (WO 00/53795) also do not have such telomerase activity :

i) Concerning the NHOK ("Normal Human Oral Keratinocytes") cells, it is pointed out that these are normal cells which have a limited life span. They exhibit telomerase activity during the proliferative phase, but telomerase activity is lost near and at senescence (see publication **Kang 1998 :** copy enclosed as EXHIBIT C). This occurs at around 19 to 20 population doublings as confirmed by Kang 1998 (see Kang, Figure 5 ; page 88, column 1; page 92 column 1). At this stage the telomerase activity of the NHOK cells is *"virtually identical to the RNase-treated negative control"* (Kang, page 88, lines 23 to 24). The cell population disclosed by Katz has a telomerase activity which is *"qualitatively equivalent"* to that of the NHOK cell line. At best, this means that the telomerase activity disappeared after 20 population doublings. In contrast, the cells of the present invention, as defined in claim 1, require that significant telomerase activity be present up to at least 130 population doublings. This characteristic is demonstrated in Example 3 of the present application (page 42 of the description). Clearly, the cells described in *Katz et al* (WO 00/53795) are not the same as the presently claimed cells.

ii) With regard to the second type of cells referred to by Katz et al (WO 00/53795) as being qualitatively equivalent in terms of telomerase activity, i.e. the bone marrow-derived mesenchymal stem cells, it is noted that the Katz priority application (US

60/162,462) refers in this context to bibliographic references "1" and "20" (see Katz priority application, page 40, line 13) :

1. Pittenger MF et al., *Multilineage potential of adult human mesenchymal stem cells*. Science 284 (5411) : 143 ; 1999
20. Prockop DJ. *Marrow stromal cells as stem cells for nonhaematopoietic tissues*. Science 276 (5309) : 71 ; 1997

Copies of these references are enclosed copy enclosed as EXHIBITS D and E, respectively. The Prockop publication (EXHIBIT E) does not refer at all to telomerase activity and is therefore irrelevant to the question of the nature of the telomerase activity in the cells disclosed by Katz et al (WO 00/53795).

The publication by Pittenger et al (EXHIBIT D) discloses that bone-marrow derived mesenchymal cells exhibit telomerase activity and that this activity is still present after 12 passages. Details of the experimental protocol (using the TRAP assay) are provided in the Supplemental Web Information (enclosed as part of EXHIBIT D) and in Web Figure 1.

Whilst Pittenger et al discloses that these cells have telomerase activity, other authors have investigated the telomerase activity of the same bone-marrow derived mesenchymal cells and have found NO such activity. For example, the enclosed publication by Zimmermann et al (2003) (EXHIBIT F) shows that the very same cells used by Pittenger[1] had, in their hands, no telomerase activity at all, despite repeated attempts. Zimmermann comments on the contradictory results obtained by Pittenger and points out that the human diploid fibroblasts used as negative control by Pittenger were actually found to be telomerase positive, suggesting an experimental error.

[1] Note in this respect that the publication by Pittenger is explicitly referred to by Zimmermann et al : see for example Zimmerman, page 1148, left hand column, final paragraph.

Thus, by reference to the Katz priority application (US 60/162,462) and to the publications cited therein, the cells disclosed in *Katz et al* (WO 00/53795) can be seen to have, at best, a telomerase activity which is lost after 20 population doublings, or alternatively, no reproducible telomerase activity at all.

Applicant therefore submits that it can be concluded from this evidence that the cells disclosed in *Katz et al* (WO 00/53795) do not have a telomerase activity which is at least 20% that of HEK293T cells and which is maintained over at least 130 population doublings. The cells disclosed in *Katz et al* (WO 00/53795) therefore do not anticipate the subject matter of the present claims.

The Examiner indicated in the Office action that the rejection may be overcome by indicating method steps not taught by *Katz et al* (WO 00/53795). The method employed in the present invention and to which reference is made in claim 25 of the enclosed claim set differs in at least the following respect over the process taught by *Katz et al* (WO 00/53795).

- the process of the present application, employs as source of the stem cells, adipose tissue obtained from a child under 10 years of age. As stated in the present application at page 7, lines 15 to 20, stem cells appear to undergo an ageing process which results in a loss of functionality therefore it is important to use tissue from young donors to ensure the presence of the multipotent cells of the invention. The process according to WO 00/53795 does not use such tissue but rather uses tissue from liposuction effluent obtained from patients undergoing elective surgery (WO 00/53795, Example 1). Such procedures are not carried out on children under 10 years of age. Consequently the tissue used as source of multipotent cells in

WO 00/53795 does not have the same composition as that used according to the invention.

- Furthermore, the process of the present invention comprises a step of selection of two sub-populations, one having an adhesion rate of less than 12 hours and the other having an adhesion rate of more than 12 hours. The stem cells of the invention occur only in the fast-adherent fraction (see present application page 9, line 12). By carrying out this separation process, loss of this rare cell type by dilution in the rest of the precursor-type cells is avoided. The process according to *Katz et al* (WO 00/53795) does not comprise such a step, and consequently the rare stem cells (as opposed to multipotent precursors), are diluted and are not present in all culture dishes in *Katz et al*.
- Lastly, the process according to the present invention comprises a step of enrichment of the fast-adhering population until a quiescent population is obtained. This step guarantees that the cells obtained are true stem cells rather than multipotent precursors which die after around 50 population doublings (see present application, page 10). Such a step is not carried out in the process according to WO 00/53795.

The process employed in the present invention is thus significantly different from that disclosed in WO 00/53795, and consequently the cells and cell populations obtained are also different. The cells disclosed in *Katz et al* (WO 00/53795) do not anticipate the subject matter of the present claims.

In view of these remarks, applicants maintain that claims 1 to 3, 49, 50, 53 and 54, and claims 4 to 7, 9 to 12, 48, 51 and 52 satisfy the requirements of 35 U.S.C. §102(b). Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

b) Zuk et al 2001 Tissue Engineering 7 : 211-228 ;

Claims 1-3, 49, 50, 53, 54 and Claims 4-7, 9-12, 48, 51 and 52 are currently rejected under 35 USC 102(b) over Zuk et al 2001.

Specifically the Examiner indicates that Applicant's arguments referring to Katz II, are not persuasive. Without conceding the correctness of the Examiner's rejection, Applicant notes that Claim 1 of the enclosed claim set has been amended to recite that the claimed cell has an endogenous β-galactosidase activity of less than 0.05% at 60 population doublings.

The cells disclosed in Zuk 2001 do not have this characteristic and consequently are not the same as the claimed cells.

Endogenous β-galactosidase activity is a measure of senescence in a cell population. A level of less than 0.05% shows that at 60 population doublings the population is not senescent, but is rather quiescent. This means that the cells are capable of undergoing a very high number of doublings without becoming senescent, and is thus an indication of "stemness".

The cells disclosed in Zuk 2001 do not have this property. Indeed, as can be seen from Figure 1C of Zuk 2001, the cells have significant β-galactosidase activity at 15 passages. This activity is confirmed at page 217, line 9 of Zuk 2001 as being **15%**. Note also that 15 passages in the method of Zuk corresponds to approximately 26 population doublings, as shown in Figure 1B of Zuk 2001. This figure shows a linear relationship between population doubling and passage number. In conclusion, the cells disclosed in Zuk 2001 have an **endogenous** β-

galactosidase activity of 15% at 26 population doublings. Consequently they will have an endogenous β-galactosidase activity much greater than 15% at 60 population doublings. **These cells therefore do NOT have the required characteristic of an endogenous β-galactosidase activity of less than 0.05% at 60 population doublings, as required by the present claims.**

The cells disclosed in Zuk 2001 do not anticipate the subject matter of the present claims.

Moreover, Applicant notes that the method disclosed in Zuk 2001 is not the same as the method employed in the present invention, and to which reference is made in claim 25.

In particular, in contrast to the process of the present invention, the process of Zuk 2001 :

- does NOT involve use of adipose tissue from a child of under ten years of age,
- does not involve the separation of the fast-adherent population from the slowly-adhering cell population, and
- does not expand the cells until quiescence is reached.

As discussed above in relation to *Katz et al* (WO 00/53795), these process steps are important in determining the nature of the cells obtained. The process of Zuk et al does not involve any of these steps and consequently the cells obtained are also different.

In view of these remarks, applicants maintain that claims 1 to 3, 49, 50, 53 and 54, and claims 4 to 7, 9 to 12, 48, 51 and 52 satisfy the requirements of 35 U.S.C. §102(b). Accordingly, applicants respectfully request the Examiner reconsider and withdraw this ground of rejection.

Supplemental Information Disclosure Statement

This Supplemental Information Disclosure Statement is to be treated as a submission under 37 C.F.R. §1.114(c) accompanying a Request For Continued Examination under 37 C.F.R. §1.114(b) being filed after receipt of a final office action.

In accordance with the duty of disclosure under 37 C.F.R. §1.56, applicants direct the Examiner's attention to the following references which are listed on the PTO-1449 (substitute) form attached hereto as **Exhibit A.** Copies of the documents listed below as items 1-5 are attached hereto as **Exhibits B-F.**

This Supplemental Information Disclosure Statement is being submitted pursuant to 37 C.F.R. §1.97(b)(4) before the mailing of a first office action after the filing of a request for continued examination under §1.114 and no fee is deemed necessary with the filing of this Supplemental Information Disclosure Statement. Thus, this Supplemental Information Disclosure Statement should be entered and considered.

1. Katz et al., U.S. Provisional Application No. 60/162,462, filed October 29, 1999 **(Exhibit B)**;

2. Kang, M.K. et al., (1998) "Replicative Senescence Of Normal Human Oral Keratinocytes Is Associated With The Loss Of Telomerase Activity Without Shortening Of Telomeres", *Cell Growth and Differentiation*, 9:85-95 **(Exhibit C)**;

3. Pittenger, M.F. et al., (1999) "Multilineage Potential Of Adult Human Mesenchymal Stem Cells", *Science* 284:143-147 **(Exhibit D)**;

4. Prockop, D.J., (1997) "Marrow Stromal Cells as Stem Cells for Nonhematopoietic Tissues", *Science* 276:71-74 **(Exhibit E)**; and

5. Zimmermann, S. et al., (2003) "Lack Of Telomerase Activity In Human Mesenchymal Stem Cells", *Leukaemia* 17(6):1146-1149 **(Exhibit F)**.

In view of the remarks hereinabove, applicants respectfully submit that the grounds of rejection set forth in the February 27, 2007 Final Office Action have been overcome. Applicants therefore respectfully request that the Examiner reconsider and withdraw these grounds of rejection and allow claims 1-7, 9-12, 25-28 and 48-54 as amended.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicants' undersigned attorney invites the Examiner to telephone him at the number provided below.

No fees, other than the enclosed $2,230.00 fee for a five-month extension of time and $810.00 RCE fee, are deemed necessary in connection with the filing of this RCE and Amendment and Supplemental Information Disclosure Statement as submissions accompanying a RCE. Accordingly, a check in the amount of $3,040.00 is enclosed. If any additional fee is required, authorization is hereby given to charge the amount of such fee to Deposit Account No. 03-3125.

Respectfully submitted,

John P. White
Registration No. 28,678
Attorney for Applicants
Cooper & Dunham LLP
1185 Avenue of the Americas
New York, NY 10036
(212) 278-0400

I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:

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Exhibit A

Exhibit B